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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2001 (07.06.2001)

PCT

(10) International Publication Number
WO 01/40236 A2

(51) International Patent Classification[7]: C07F 9/09, 9/6558, C07D 413/14, 413/12, C07F 9/6574

(21) International Application Number: PCT/GB00/04527

(22) International Filing Date:
28 November 2000 (28.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9928499.4 3 December 1999 (03.12.1999) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/40236 A2

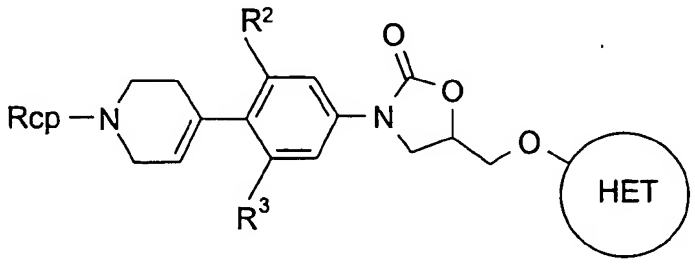
(54) Title: CHEMICAL PROCESSES AND INTERMEDIATES

(57) Abstract: The invention relates to chemical processes and chemical intermediates which are useful in the selective formation of a primary mono-phosphoryl group (-OPO(OH_2)) in a terminal 1,2-diol-propanoyl (HO-CH_2CH(OH)-CO-) containing system, and to chemical processes and chemical intermediates (and processes for their manufacture) particularly useful for the manufacture of anti-Gram positive oxazolidinone bacterial agents containing such functionality, in particular for the preparation of 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hychoxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-il)3,5-difluorophenyl)oxazolidin-2-one.

CHEMICAL PROCESSES & INTERMEDIATES

The invention relates to chemical processes and chemical intermediates. More particularly, it relates to processes and intermediates which are useful in the selective formation of a primary mono-phosphoryl group in a terminal-1,2-diol-propanoyl containing system, most particularly certain oxazolidinone anti-Gram positive bacterial agents containing such functionality. The invention also relates to processes for the manufacture of said intermediates and to processes for the manufacture of such oxazolidinone compounds utilising said intermediates.

Co-pending International Patent Application No. GB99/01753 (WO 99/64417) describes a new class of antibacterial oxazolidinone compounds which are effective as anti-Gram positive bacterial agents, and certain processes for their preparation. Of the compounds disclosed, those of the formula (I) are included :



(I)

wherein

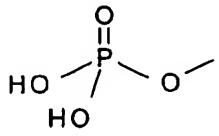
HET is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

R^2 and R^3 are independently hydrogen or fluoro;

Rcp is of the formula $R^{13p}CO$- (wherein R^{13p} is (1-10C)alkyl substituted by two or more hydroxy groups; 2 of which are in a 1,2-diol orientation, ie. there is a terminal primary alcohol with an adjacent secondary alcohol), or pharmaceutically-acceptable salts, or in-vivo-hydrolysable esters thereof.

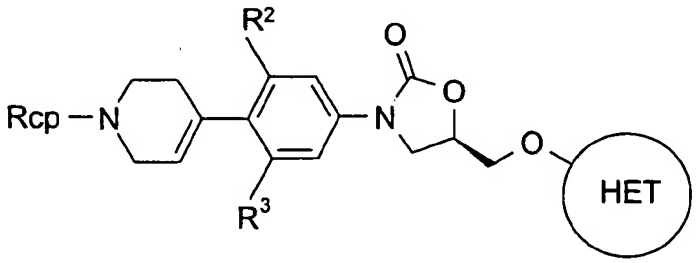
Of the above compounds, those in which HET is (unsubstituted) isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl are preferred.

In-vivo hydrolysable esters include compounds of formula (I) and (I-1) in which any free hydroxy group independently forms a phosphoryl ester of the formula (PD3) :



(PD3)

Of the compounds of formula (I), those of formula (I-1) are the pharmaceutically active anti-bacterial enantiomer. The pure enantiomer depicted in (I-1), or mixtures of the 5R and 5S enantiomers, for example a racemic mixture are included in GB99/01753. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted below is the 5R enantiomer.



(I-1)

Furthermore, some compounds of the formula (I) and (I-1) may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereo-isomers, and racemic mixtures, that possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity.

Of the above compounds of formula (I) and (I-1), 5(R)-isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (hereinafter the "said compound") is especially preferred.

The preparation of the said compound is described within GB99/01753, and the preparation is illustrated in the accompanying Scheme herein (titled "Existing Route"). The

preparation described includes isolation of the primary mono-phosphoryl compound (Intermediate Example 15) from a mixture of compounds (including, for example, the bis-phosphoryl and cyclic phosphoryl compounds) by use of Medium Pressure Liquid Chromatography using ethyl acetate as the eluant. Other compounds of formula (I) and (I-1) above may be prepared using analagous chemistry. The detailed chemistry and reaction conditions employed is described in the accompanying non-limiting Examples, or is within the skill of the ordinary organic/medicinal chemist (see also WO 97/30995, the relevant process sections of which are incorporated herein, for details on prepartion of certain intermediates).

Co-pending International Patent Application No. GB99/01753 discloses that for a compound of formula (I) and (I-1) containing a number of free hydroxy groups, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-dimethylsilyl group), and later deprotected. Also, enzymatic methods may be used to selectively phosphorylate or dephosphorylate alcohol functionalities. The prodrugs containing groups (PD3) may be prepared by reaction of a compound of formula (I) and (I-1) containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

The "Existing Route" to the said compound, although satisfactory, is not particularly suitable for the manufacture of large quantities of such products. There are a large number of chemical stages, and as such, losses in yield at each stage can contribute to the overall yield of final product being non-optimal. Selectivity of reaction is important and can impact upon the yield of desired product obtained. Poor selectivity can also lead to the formation of undesired by-products which require removal. There is therefore a need to devise chemical routes which are efficient and make good use of raw materials and intermediates. In particular, the "Existing Route" has potential difficulties associated with the selective formation, in good yield, of the primary mono-phosphoryl/secondary hydroxy moiety. Such preparation difficulties are encountered in the preparation of any primary mono-phosphoryl group in a terminal-1,2-diol-propanoyl containing system.

Apart from the "Existing Route", other routes to the said compound (and by analogy to other compounds of formula (I) and (I-1)) are possible. These include, for example,

(i) a final stage reaction of 3-hydroxyisoxazole with the 5-hydroxymethyl-oxazolidinone (with the left-hand side of the molecule assembled);

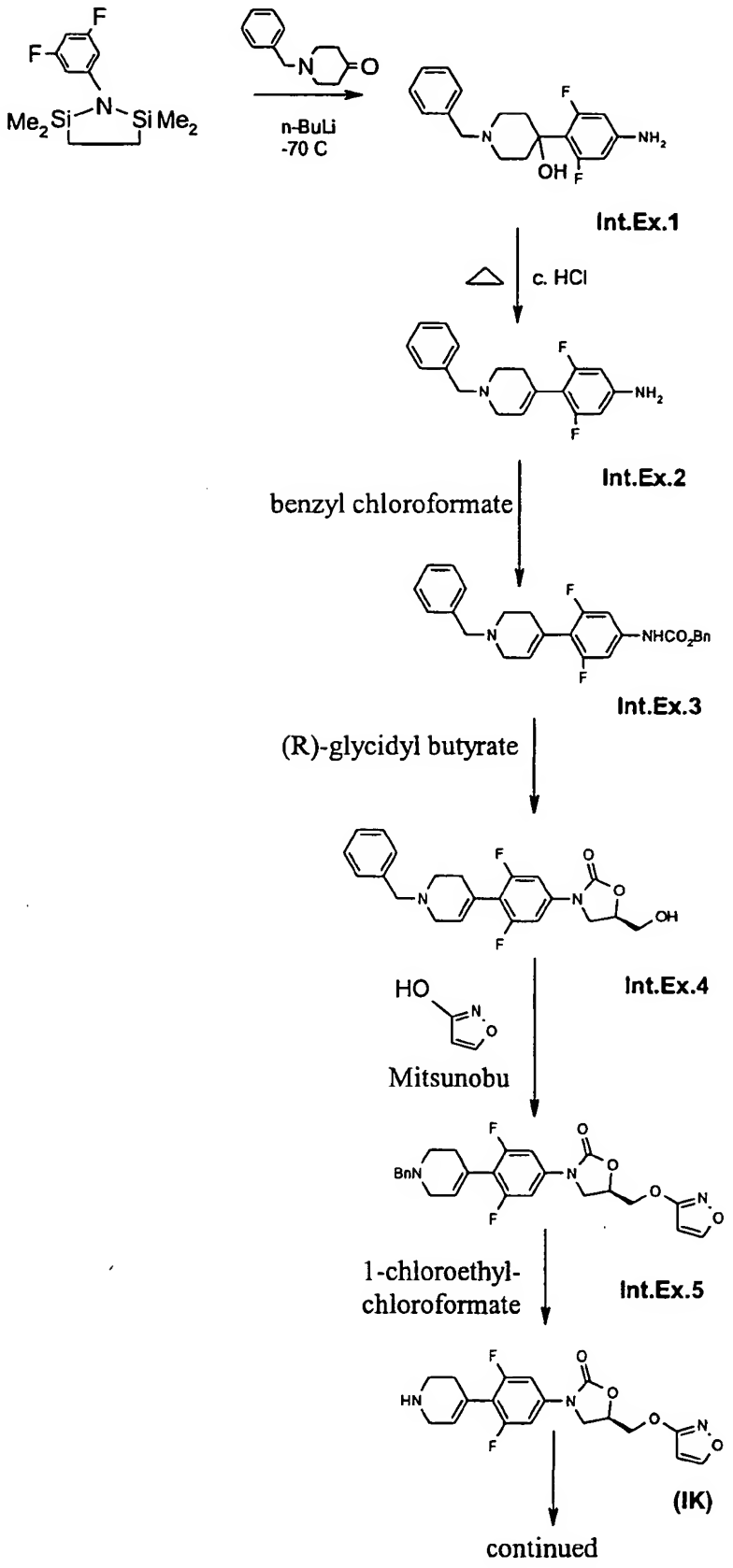
(ii) the reaction of the left-hand side piperidine (having a 4-triflate or 4-enol phosphate group) with a 4-phenyl metallated oxazolidinone (such as a 4-tin compound with the right-hand side of the molecule assembled) using Pd or Ni coupling chemistry;

(iii) the reaction of a left hand side pyridine (or pyridine N-oxide) having, for example, a 4-chloro leaving group, with a 4-(metallo)-phenyl oxazolidinone (with the right-hand side of the molecule assembled), followed by reduction of the pyridine to a 1,2,5,6-tetrahydropyridine;

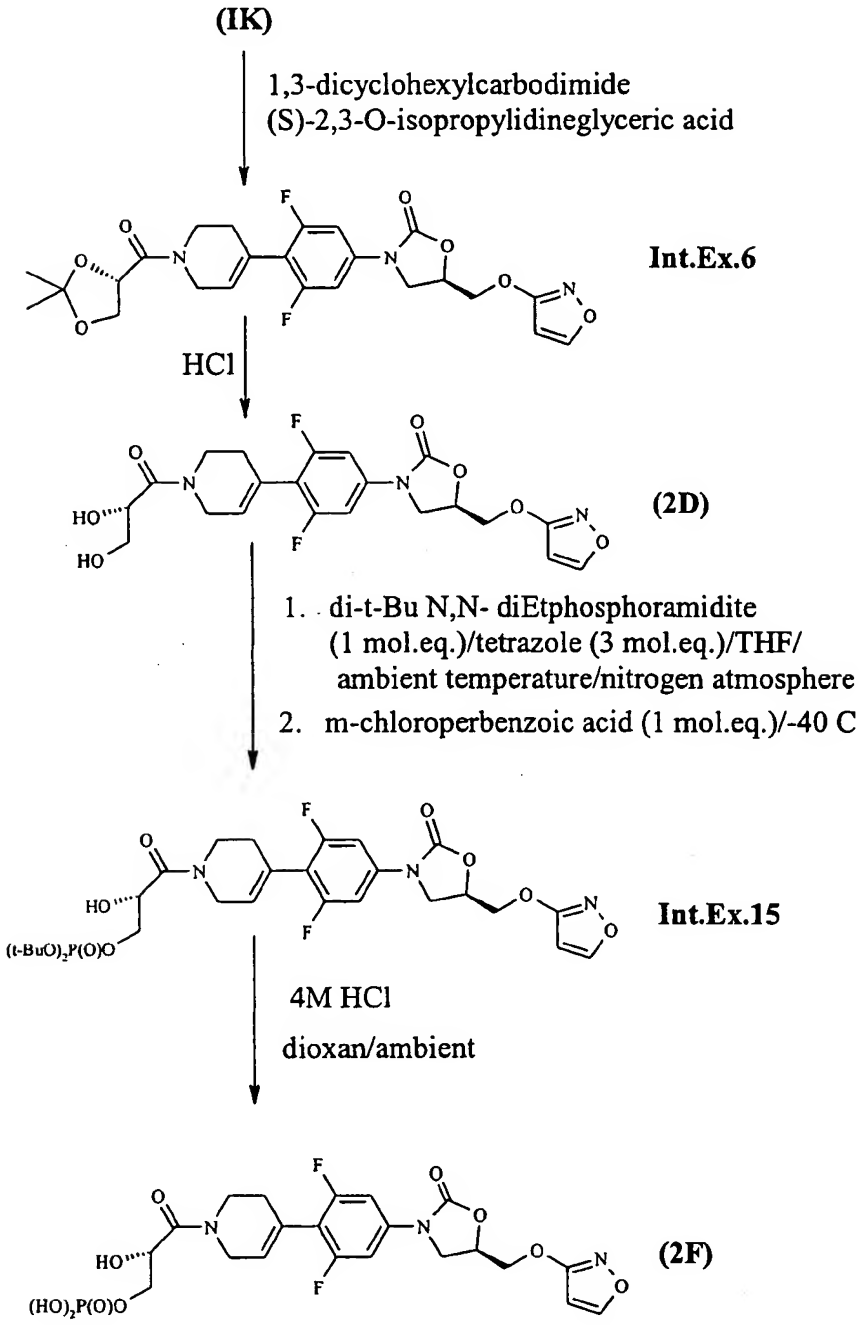
(iv) the reaction of a left hand side pyridine having a 4-boronic acid group, with a 4-(leaving group)-phenyl oxazolidinone (with the right-hand side of the molecule assembled) using Pd chemistry, followed by reduction of the pyridine to a 1,2,5,6-tetrahydropyridine.

Suitable leaving groups include halo (e.g. iodo, bromo; chloro), triflate or enol phosphate.

Scheme - Existing R ute



Scheme - Existing Route (continued)



Notes :

1. The protected aniline used as the initial starting material may alternatively be protected as -N-[SiR_3]$_2$ where each R is independently a (1-4C)alkyl group, eg. -N-($SiMe_3$)$_2$.

We have now discovered a number of further, convenient and useful, processes for the manufacture of said compound (and by analogy other compounds of formula (I) and (I-1)), which reduces and/or converges the number of reaction stages and, reduces or removes the need for chromatographic purification of intermediates and/or final products. The invention also relates to the application of the chemistry described herein to any system requiring formation of a primary mono-phosphoryl group in a terminal-1,2-diol-propanoyl containing system (such as, for example, 2,3-dihydroxypropanoyl and 3,4-dihydroxy-2-oxo-butyl). In particular, the invention relates to such 1,2-diol-propanoyl containing systems in a compound of formula (I) and (I-1), and most particularly to the said compound.

The invention also relates to 1,2-diol-propanoyl containing systems in a compound of formula (I) and (I-1) wherein HET is a C-linked 6-membered heteroaryl ring containing 1 or 2 N, which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen. Preferred 6-membered heteroaryl rings are pyridin-2-yl, pyridazin-3-yl or pyrazin-2-yl.

The invention also relates to 1,2-diol-propanoyl containing systems in a compound of formula (I) and (I-1) wherein HET is a C-linked 5- or 6-membered heteroaryl ring as described herein, wherein the link to the oxazolidinone ring is via a thiomethyl ($-CH_2-S-$) link rather than an oxymethyl ($-CH_2-O-$) link (see claim 2 for compounds of formula(I-2)).

The invention may also be used in 1,2-diol-propanoyl containing systems in a compound of formula (I) and (I-1) wherein HET is a C-linked 5- or 6-membered heteroaryl ring as described in WO 00/21960 (incorporated herein by reference), wherein the link to the oxazolidinone ring is via an aminomethyl ($-CH_2-NH_2-$) link.

In the accompanying Schemes, the conditions indicated are for illustration. In the Schemes, protecting groups have been referred to. For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be used and removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum

disturbance of groups elsewhere in the molecule.

Intermediates (Schemes 1A to 1C)

In one embodiment there are provided certain useful intermediates, and processes for the preparation of these, in particular, the compounds (IE), (IF) and (IK), and the Schemes shown in 1A, 1B and 1C. The Schemes may be genericised to cover other analogous compounds of formula (I) and (I-1).

Diol chemistry (Schemes 2A to 2C)

In another embodiment there is provided a process for the preparation of 5(R)-isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (the "said compound" - (2F)) comprising the steps illustrated in any one of the accompanying Schemes 2A to 2C.

The Schemes may be genericised to cover other analogous compounds of formula (I) and (I-1) and (I-2) mentioned herein (see claim 2 for (I-2)). Furthermore, the invention also relates to the application of the chemistry described herein to any system requiring formation of a primary mono-phosphoryl group ($-OPO(OH)_2$) in a terminal-1,2-diol-propanoyl ($HO-CH_2CH(OH)-CO-$) containing system.

A particularly preferred process is that illustrated in Scheme 2B. Thus, the use of the hydroxy acid (2H) allows the formation of a protected primary 1,2-diol species ($PgO-CH_2CH(OH)-CO-$, wherein Pg is a protecting group suitable for protecting alcohols and removable by acid, such as, for example, t-butyl, as in Compound (2I) in the case of the said compound). This then permits formation of the secondary phosphoryl compound (which may be optionally protected, for example in the form of a phosphate ester, such as the t-butyl ester as in Compound (2J) in the case of the said compound). Upon treatment with acid the protected primary alcohol is deprotected and the secondary phosphoryl compound (deprotects as appropriate and) rearranges favourably (possibly via a cyclic intermediate) to the primary phosphoryl compound to give a $(HO)_2OPO-CH_2CH(OH)-CO-$ functionality (Compound (2F) in the case of the said compound).

In a preferred embodiment the secondary phosphoryl compound is in the form of a phosphate ester. A secondary phosphoryl compound suitable for use in the process may be obtained, for example, by standard phosphorylation chemistry, for example as described

herein, using tert-butyl tetraethylphosphorodiimidite, or using phosphorous oxychloride or $(EtO)_2POCl$.

Coupling chemistry (Schemes 3A to 3D)

In a further embodiment there is provided a process for the preparation of 5(R)-isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one comprising the steps illustrated in any one of the accompanying Schemes 3A to 3D. The Schemes may be genericised to cover other analogous compounds of formula (I) and (I-1) and (I-2) mentioned herein.

Scheme 3C is particularly preferred, and offers the advantageous use of the hydroxy acid (2H) to give the protected primary alcohol, and then selective secondary phosphorylation to give (3D); followed by coupling, and then by deprotection of the protected primary alcohol & predominant rearrangement of the secondary phosphoryl compound to the primary phosphoryl compound. Overall, Scheme 3C offers a particularly favourable route to the said compound, comprising comparatively few reaction stages in a convergent fashion.

The coupling reaction of Schemes 3A to 3D may be carried out in the presence of a suitable base, for example, nBuLi at ca. -70^{0}C, in a suitable inert solvent or diluent, such as, for example, dimethylsulphoxide, 1,2-dimethoxyethane, tetrahydrofuran (THF), tetrahydropyran, diglyme or toluene. A preferred solvent is a mixture of THF and toluene. The reaction is conveniently performed at a temperature in the range, for example, -100 to -70°C, conveniently at or near -70°C.

The coupling of Schemes 3A to 3D may also be achieved via Grignard chemistry, using, for example, an appropriate 4-bromo-phenyl compound in place of (IF).

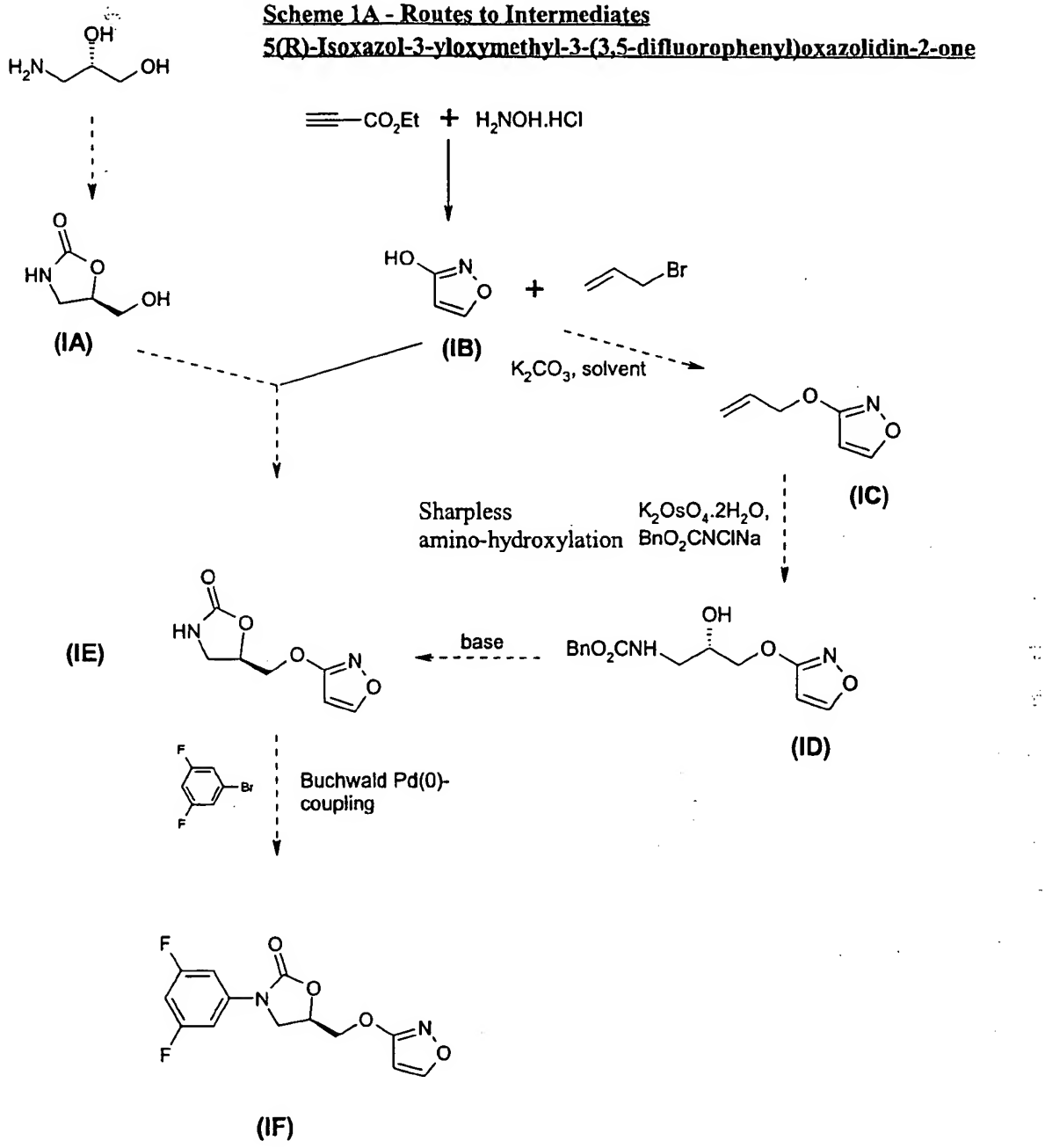
The starting materials for the reactions described herein may be obtained as described herein, or by analogy to such methods, or by standard procedures of organic chemistry.

The processes and intermediates described herein are illustrated within the accompanying non-limiting Examples which are provided for the purpose of illustration only.

According to a further feature of the invention there is provided the use of an intermediate as described herein for the manufacture of a compound of formula (I) and (I-1) (or of the said compound).

Scheme 1A - Routes to Intermediates

5(R)-Isoxazol-3-yloxymethyl-3-(3,5-difluorophenyl)oxazolidin-2-one



Notes :

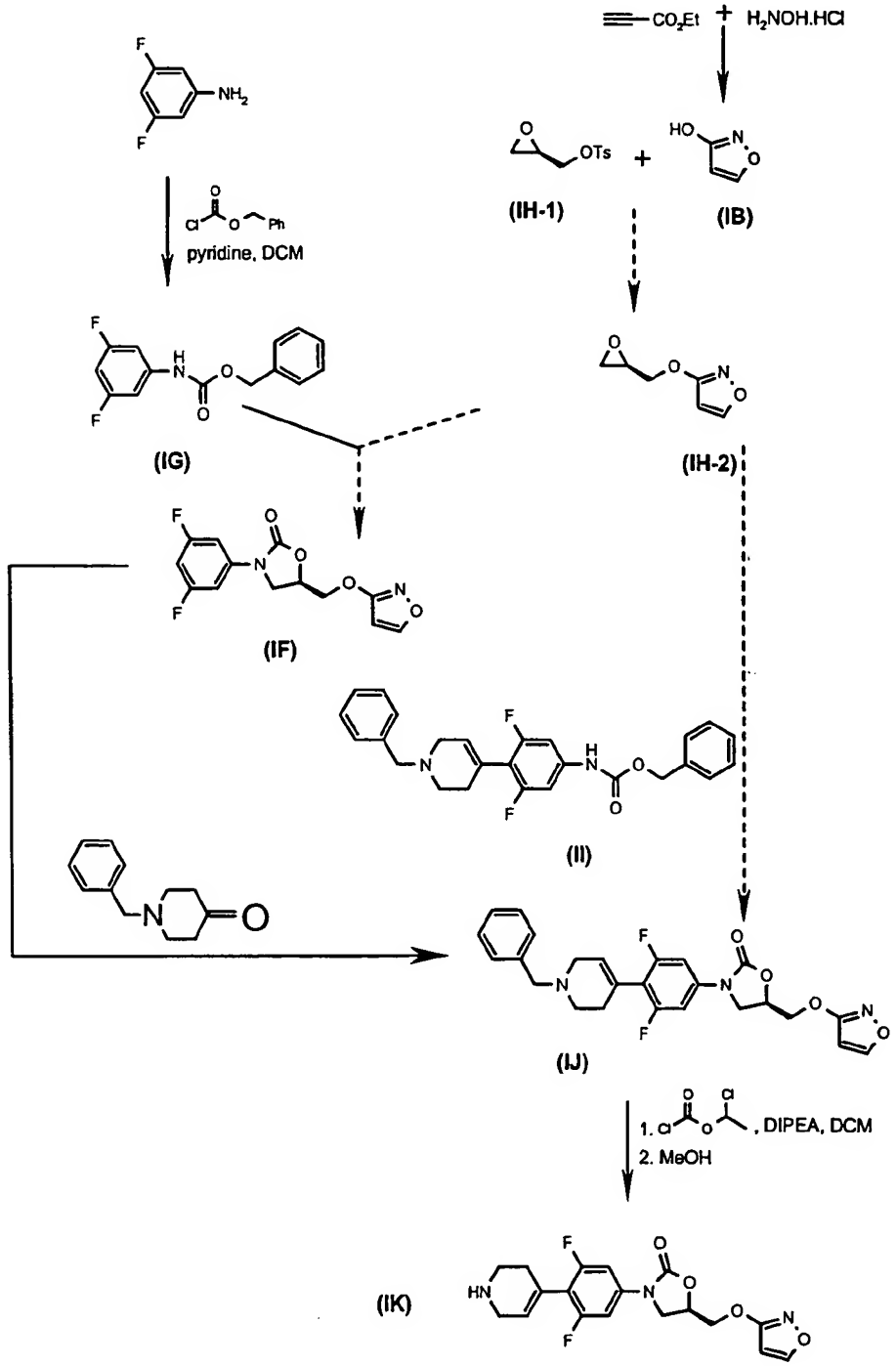
1. Intermediates (IE) and (IF) are preferred intermediates, especially (IF).

2. In the reaction of (IB) to (IC), and of (IE) to (IF), a leaving group other than Br could also be used. For the reaction of (IB) to (IC), allyl alcohol could be used and the substitution performed in a reverse sense to that shown with a leaving group (e.g. chloro or mesylate) on (IB).

Scheme 1B - Routes to Intermediates

5(R)-Isoxazol-3-yloxymethyl-3-(3,5-difluorophenyl)oxazolidin-2-one

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one



Notes :

1. Nosylate and mesylate may also be used in place of tosylate in the epoxide (IH-1). Preferably nosylate is used.

2. Protecting groups other than benzyl (e.g. t-BOC) may also be used in compounds (II) & (IJ).

3. Chiral integrity of (IH) and (IF) may be determined by chiral HPLC or chiral shift nmr.

4. For details on preparation of (IB) see Example 1 hereinafter.

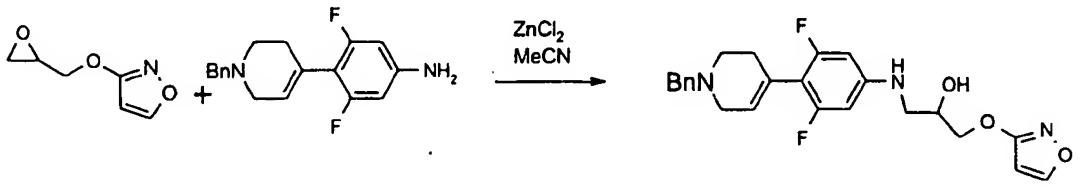
In the reaction of (IB) with the epoxide (IH-1) Example 1 hereinafter shows retention of stereochemistry, i.e. (R)- and (S)-glycidyl nosylate give, respectively, (R)-, (S)-glycidyl ether product. However, if chirality is not retained in such a reaction then the other epoxide isomer may be used as a starting material. If a racemate is obtained, chiral resolution/chromatography may be used to obtain the desired isomer.

5. The reaction of (IG) with (IH-2) is performed in the presence of a base such as n-BuLi. Weaker bases are to be preferred, such as triethylamine, Triton-B (TM) and CsF (see Tetrahedron, 55, 14381 (1999)).

6. DIPEA is di-isopropyl-ethylamine.

Scheme 1C - Routes to intermediates

1-[4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenylamino]-3-(isoxazol-3-yloxy)-propan-2-ol

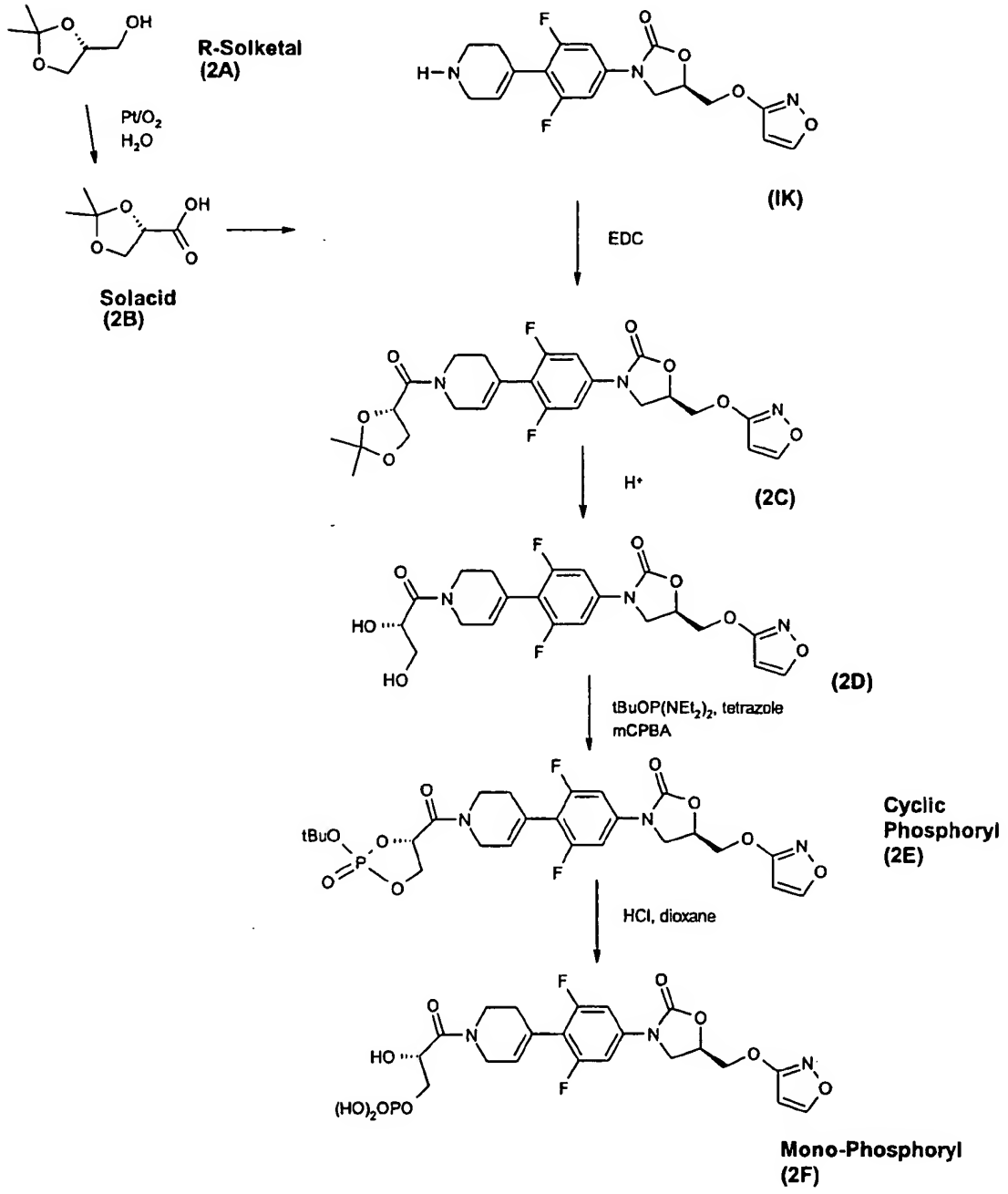


(IH-2) **(IN)**

Notes :

1. (IN) may be treated with, for example, phosgene or dimethylcarbonate to form the oxazolidin-2-one ring.

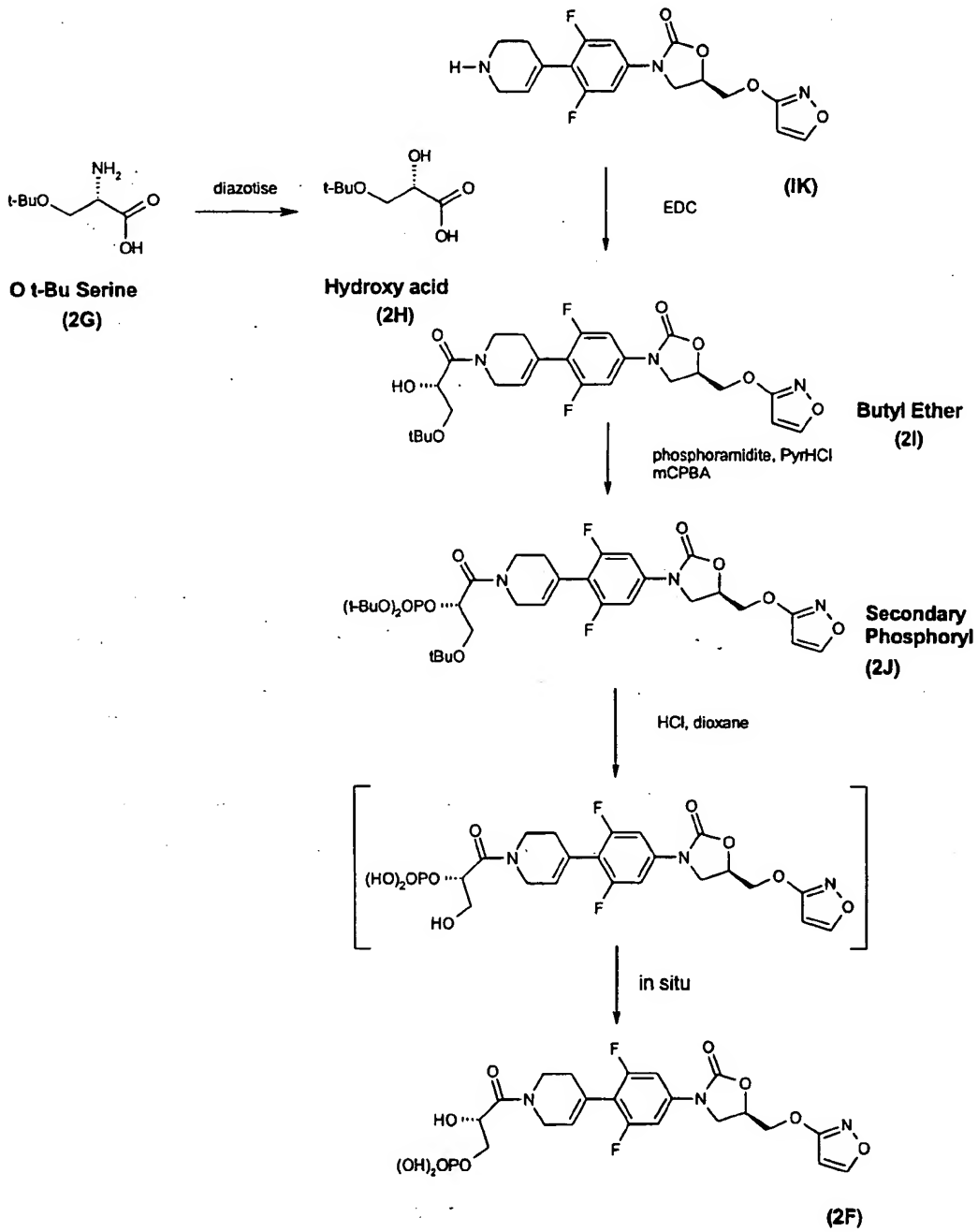
Scheme 2A - Diol Chemistry ; Route to diol and cyclic phosphoryl chemistry



Notes :-

1. The opening of the cyclic phosphoryl (2E) provides for predominant selectivity as the monophosphoryl compound (e.g. 85 : 15 - primary : secondary).

Scheme 2B - Diol Chemistry : Route to protected diol and rearrangement t primary mono-phosphoryl



Notes :

1. The reaction of (2G) to (2H) is performed under standard conditions, with retention of stereochemistry. The diazotisation reaction may be performed using aqueous

sulfuric acid and aqueous sodium nitrite at ambient temperature. Quenching with sulfamic acid, extraction with TBME and washing with brine gives the (2H) product.

2. The use of the hydroxy acid allows the formation of a protected primary 1,2-diol species. This permits the formation of the secondary phosphoryl compound (2J). Upon treatment with acid (e.g. 4M HCl at ambient temperature) this secondary phosphoryl compound rearranges favourably (possibly via a cyclic intermediate) to the primary phosphoryl compound (2F). The rate of rearrangement is dependant on acid concentration and temperature.

3. Other non-bulky protecting groups in place of t-Bu may be used in (2G) and (2H), for example, any (1-4C)alkyl group; any silyl group (for example trimethylsilyl); or a benzyl group (e.g. using acid catalysed removal, or a reductive removal using e.g. hydrogenation).

4. (2F) may be converted at ambient temperature to, for example, the disodium salt by treatment with 2 mol.eq. sodium carbonate and working-up in acetone and then IMS.

5. (IK) may be prepared as shown in the Existing Route Scheme or as described in Example 4 hereinafter, in which, for example, Intermediate Example 2 may be prepared as follows :-

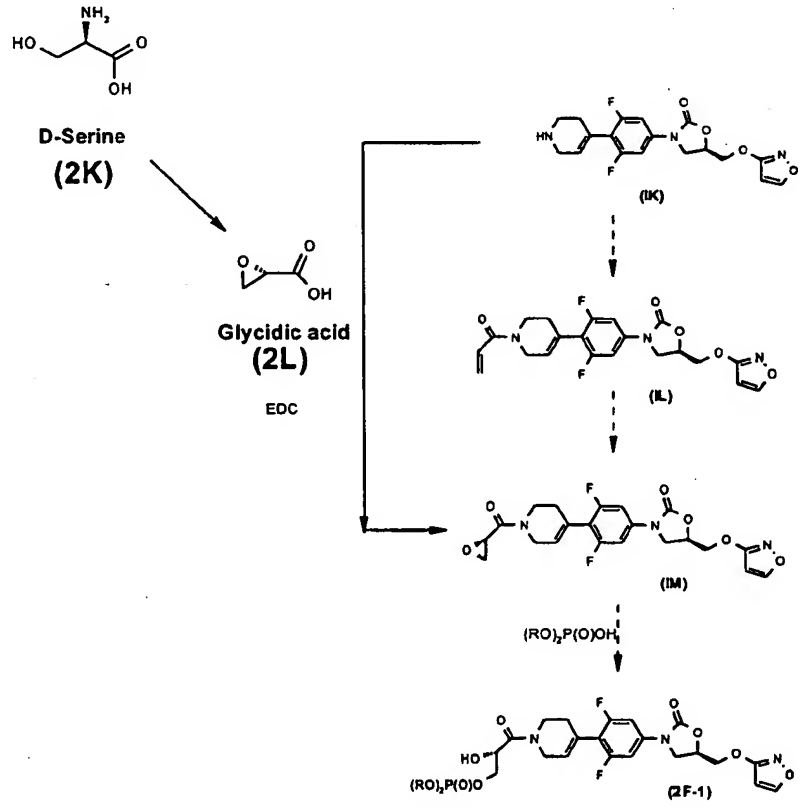
A solution of 3,5-difluoroaniline in THF is chilled to -70°C. A solution of n-butyl lithium in toluene is added and chlorotrimethylsilane then added to complete the bis-trimethylsilyl protection of 3,5-difluoroaniline. A solution of n-butyl lithium in toluene is added to the chilled solution and a solution of 1-benzyl-4-piperidone in toluene then added whilst maintaining the temperature. When the reaction is complete, after warming to near ambient temperature a solution of aqueous hydrochloric acid is added. The aqueous layer of the alcohol intermediate (Intermediate Example 1) is separated and heated to reflux while simultaneously distilling out tetrahydrofuran to complete the formation of Intermediate Example 2. The reaction is then diluted with water and butanol before adjusting the pH with aqueous ammonia at 40°C. The aqueous layer is separated and discarded. Cyclohexane is added to the organic phase to precipitate the product, which is then filtered off after cooling to ambient temperature, washed with a butanol/cyclohexane mixture, cyclohexane and dried under vacuum.

Intermediate Example 4 may be prepared as described in Example 4 hereinafter, or using a solution of n-butyl lithium in toluene.

6. (2I) may be converted to Diol (2D) by deprotection, for example using acid conditions, such as HCl/dioxan.

7. Hydrogen peroxide may be used in place of mCPBA in the conversion of (2I) to (2J). The reaction is performed in a suitable solvent, such as dioxan.

Scheme 2C - Diol Chemistry : Route to primary mono-phosphoryl



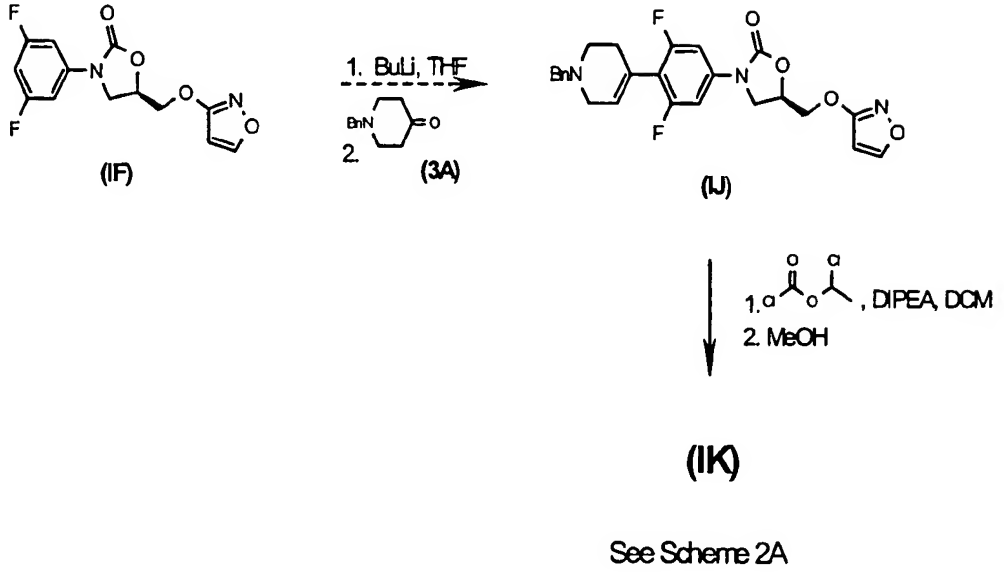
Notes :

1. R includes (1-4C)alkyl, for example, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl; hydrogen and benzyl.

In this specification the generic term "(1-4C)alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to any other generic terms.

2. The reaction with the epoxide (1M) gives predominantly the primary phosphoryl compound.

Scheme 3A - Coupling Reaction 1



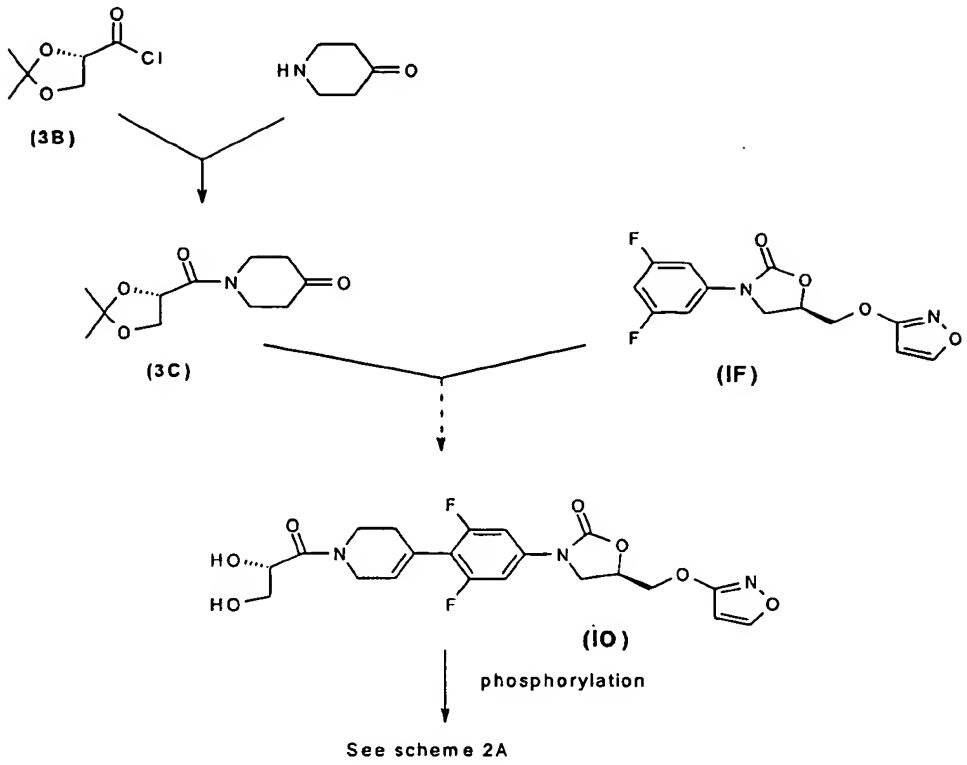
See Scheme 2A

Notes :

1. In the reaction of (IF) with (3A), other metallating agents other than BuLi may be used (for example, LDA).

2. In the reaction of (IF) with (3A), after treatment of (IF) with BuLi the lithiated compound may be transmetallated with, for example titanium chloride, titanium i-propoxide or cerium chloride at a tempertaure of about -30°C. Such transmetallation restricts enolisation of the piperidinone and so aids reaction at the desired centre.

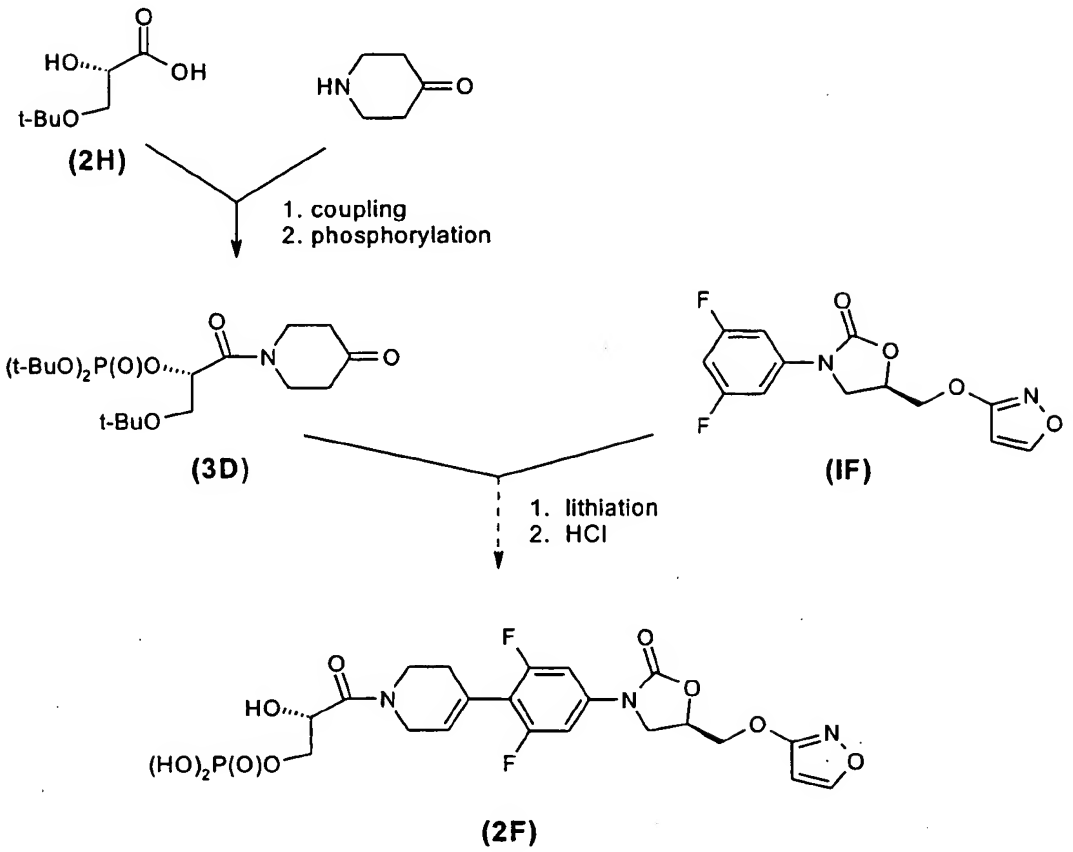
Scheme 3B - Coupling Reaction 2



Notes :

1. (3B) may be prepared from (2B) - see scheme 2A - using standard chemistry.

Scheme 3C - Coupling Reaction 3

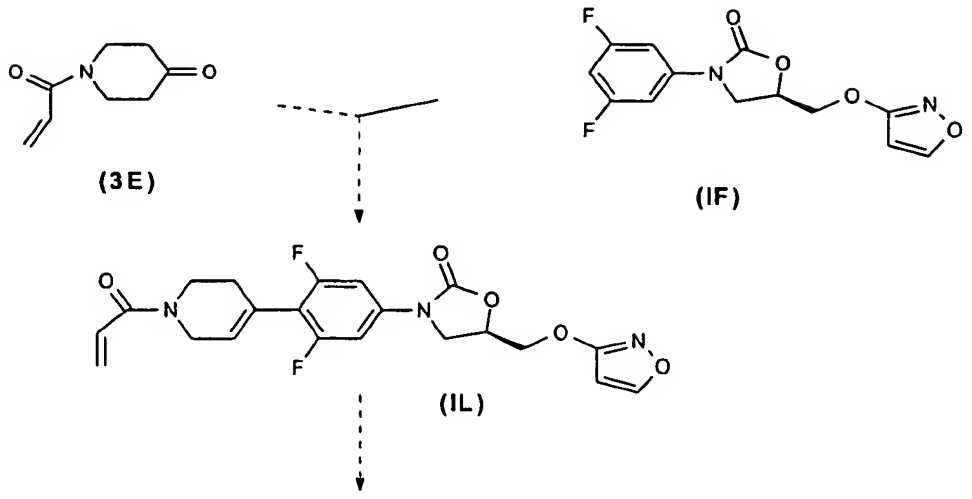


Notes :

1. (2H) may be prepared from O-t-Bu-serine (2G) using standard chemistry - see Scheme 2B.

2. A cyclic phosphoryl equivalent of (3D) may also be used, which (after the coupling reaction) is then opened to give the primary mono-phosphoryl compound (see Scheme 2A). (3D) is a preferred Intermediate.

Scheme 3D - Coupling Reaction 4



As Scheme 2C to give (2F)

The invention is illustrated, but not limited, by the following Examples in which (hereinbefore and hereinafter) unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and in air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the formula (I) and (I-1) were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-D6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform

spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected];

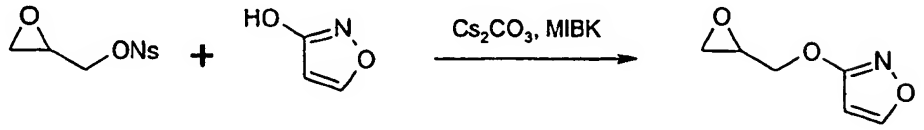
(vi) intermediates were not generally fully characterised and purity was in general assessed by thin layer chromatographic, infra-red (IR), mass spectral (MS) or NMR analysis; and

(vii) in which the following abbreviations may be used :-

® or TM is a Trademark; DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; DCM is dichloromethane; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is mass spectroscopy; ESP is electrospray; THF is tetrahydrofuran; TFA is trifluoroacetic acid; NMP is N-methylpyrrolidone; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is $(HO)_2$-P(O)-O-; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (hydrochloride); PTSA is para-toluenesulfonic acid; DIPEA is di-isopropyl-ethylamine; TBME is t-butylmethylether.

Example 1 : Preparation of intermediates - Scheme 1B

Preparation of 3-(2,3-oxiranepropyloxy)isoxazole (Compound (IH-2))



A suspension of caesium carbonate (45.7g, 140 mmol, 1.2 equiv), 3-hydroxyisoxazole (11.9g, 140 mmol, 1.2 equiv) and glycidyl nosylate (30.2g, 116 mmol, 1.0 equiv) in isobutyl methyl ketone (MIBK, 302 mL) was heated at reflux for 30 min (HPLC indicated complete reaction). The reaction mixture was cooled to 20-25 °C, filtered and the filtrate washed with H_2O (151 mL). The organic layer was concentrated to give the glycidyl ether product (10.8 g, 66%) as an orange oil.

^{1}H-NMR ($CDCl_3$): delta = 2.74 (dd, 1H, J = 2.6 & 4.9 Hz), 2.91 (dd, 1H, J = 4.1 & 4.9 Hz), 3.37-3.41 (m, 1H), 4.14 (dd, 1H, J = 11.8 & 6.4 Hz), 4.60 (dd, 1H, J = 11.8 & 2.8 Hz), 6.00 (d, 1H, J = 1.8 Hz), 8.14 (d, 1H, J = 1.8 Hz).

^{13}C-NMR ($CDCl_3$): 44.5, 49.4, 70.6, 76.6, 96.1, 159.8, 171.2.

HPLC : retention time 3.2 min.

The following HPLC method was used :-

Mobile phase A: 10 mM ammonium acetate pH 4.5. Mobile phase B: 10 mM ammonium acetate pH 4.5 in 90% acetonitrile. Column: Zorbax SB-CN, 4.6mm x 15cm. Flow rate 1.5 ml/min, stoptime 8 min, postime 5 min. Gradient: 0 min - 5%B, 3 min - 5%B, 8 min - 100%B. Wavelength: 225 nm Bw 4 nm, reference wavelength 400 nm, bw 80 nm. Injection 2.5 ul. Sample solvent: 50:50 acetonitrile:water. conc. up to 1mg/ml. Oven: 45°C.

The reaction has been performed using both (R)- and (S)-glycidyl nosylate as well as racemic glycidyl nosylate to give, respectively, (R)-, (S)- and racemic glycidyl ether product, i.e. retention of stereochemistry was confirmed (using chiral HPLC and NMR).

The following solvents have also been used in the coupling reaction in place of MIBK:- DMF, acetone, toluene, MeCN, DME, NMP, THF, EtOAc, TBME, EtOH, MeOH.

The following bases have also been used in the coupling reaction in place of caesium carbonate:- NaH, K_2CO_3, NaOH, NaOMe, NaOEt, KOMe, KOEt, KO^{t}Bu, LDA, NEt_3, NBu_3, N^{i}Pr$_2$Et.

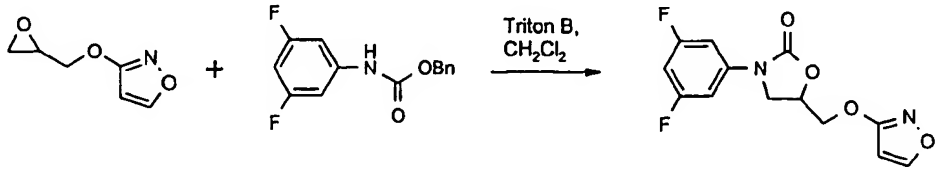
The starting materials are commercially available. 3-Hydroxyisoxazole may be prepared by cyclisation of CH≡C-CO-NHOH (prepared from CH≡C-CO-O-(1-4C)alkyl) as described in Chem.Pharm.Bull.Japan, 14, 92, (1966). For further information, see also JP 43014704 (1968), FR 1534601 (1968), DE 1918253 (1970), JP 45038327 (1970), DE 1795821 (1980) & WO 94/18201 (Sankyo) and DE 2251910 (1973) (Nippon Chem. Ind.).

For example, 3-Hydroxyisoxazole may also be prepared as follows :-

Hydroxylamine hydrochloride is neutralised with sodium hydroxide to liberate the free base. Ethyl propiolate in EtOH is then added dropwise maintaining the reaction temperature at 20-25°C and the reaction stirred before gradually warming to 50-55°C. Heating is continued at 50-55°C for 2.5h and the reaction is then acidified to pH ~3 with conc. HCl. On complete addition ca. 90% of the ethanol in the reaction is removed by distillation and the residue extracted with warm toluene. Toluene is removed by distillation to precipitate 3-hydroxyisoxazole, and the precipitation is completed by addition of cyclohexane. The resulting suspension is cooled and filtered prior to the material being dried in vacuo at ambient temperature.

Alternatively, hydroxylamine hydrochloride is neutralised with sodium hydroxide. The hydroxylamine free base is reacted with a solution of ethyl propiolate in THF at 55 °C. The reaction mixture is cooled and acidified with hydrochloric acid, and the resulting solution extracted with butyronitrile, washed with dilute hydrochloric acid and the organic solution concentrated under reduced pressure to remove ethanol, THF and water. The solution may be used directly in a next stage.

Preparation of 5-Isoxazol-3-yloxymethyl-3-(3,5-difluorophenyl)oxazolidin-2-one (Compound (IF))



To (3-(2,3-oxiranepropyloxy)isoxazole; 0.6g, 4.2 mmol, 1.1 equiv) and N-benzyloxycarbonyl-3,5-difluoroaniline (1.0g, 3.8 mmol) in DCM (15 mL) was added Triton-B (TM) (0.1 mL, 0.76 mol, 40% in H_2O). The reaction mixture was heated for 10 hr at reflux. On completion, the reaction mixture was cooled to 20-25 °C, diluted with DCM (10 mL) and was washed with H_2O (10 mL). The organic layer was separated, dried ($MgSO_4$) and was concentrated to give crude product (1.4 g) which was purified by flash chromatography to give the desired product (0.8g, 71 %).

^{1}H-NMR ($CDCl_3$): d = 3.95 (dd, 1H, J = 6.4 & 8.9 Hz), 4.13 (dd, 1H, J = 9.0 & 8.9 Hz), 4.51 (dd, 1H, 4.4 & 11.7 Hz), 4.60 (dd, 1H. J = 3.9 & 11.7 Hz), 5.00 – 5.07 (m, 1H), 6.00 (d, 1H, J = 1.9 Hz), 6.61 (dt, 1H, J = 1.9 & 11.0 Hz), 7.1 – 7.2 (m, 2H), 8.16 (d, 1H, J = 1.9 Hz).

HPLC : retention time (method as above) 7.6 min.

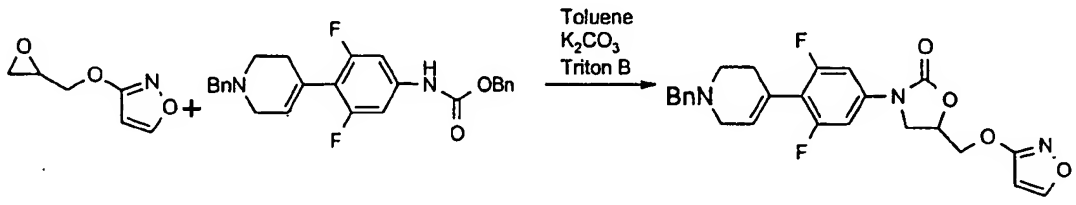
The following solvents have also been used in the coupling reaction in place of DCM:- MIBK, THF, Toluene, TBME.

N.B.: There is retention of stereochemistry in the reaction, i.e. (R)-glycidyl ether gives 5(R)-Isoxazol-3-yloxymethyl-3-(3,5-difluorophenyl)oxazolidin-2-one.

The N-benzyloxycarbonyl-3,5-difluoroaniline intermediate is prepared by reaction of 3,5-difluoroaniline with benzyl chloroformate (1.5 mol.eq.) as shown in Scheme 1B (at 0 °C to ambient) in 5 vol. EtOAc/5 vol. water, using potassium carbonate base (2 mol.eq.).

Example 2 : Preparation of intermediates - Scheme 1B

Preparation of 5-Isoxazol-3-yloxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (Compound (JJ))



To (3-(2,3-oxiranepropyloxy)isoxazole (1.0g, 7.1 mmol, 1.2 equiv) and N-benzyloxycarbonyl-3,5-difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline (2.6g, 6.0 mmol) in toluene (15 mL) was added tetrabutylammonium chloride (0.18 g, 0. 6 mmol) and

potassium carbonate (0.83g, 6 mmol). The reaction mixture was heated for 24 hr at reflux. On completion, the reaction mixture was cooled to 20-25 °C, and was washed with H_2O (20 mL). The organic layer was separated, dried ($MgSO_4$) and was concentrated to give crude product that was purified by flash chromatography to give the desired product (IJ) (1.5g, 53 %).

^{1}H-NMR ($CDCl_3$): d = 1.60 (s, 2H), 2.43 (s, 2H), 2.71 (t, 2H, J = 6.0 Hz), 3.18 (m, 2H), 3.65 (s, 2H), 3.95 (dd, 1H, J = 6.4 & 8.9 Hz), 4.13 (dd, 1H, J = 9.0 & 8.9 Hz), 4.51 (dd, 1H, 4.4 & 11.7 Hz), 4.60 (dd, 1H. J = 3.9 & 11.7 Hz), 5.00 – 5.07 (m, 1H), 5.82 (s, 1H), 6.00 (d, 1H, J = 1.9 Hz), 7.12 – 7.40 (m, 7H), 8.14 – 8.16 (m, 1H).

HPLC : retention time (see below) 5.3 min.

Mobile phase A: 0.1% TFA in water. Mobile phase B: 0.1% TFA in 90 % MeCN.

Column: Genesis C18 10 x 0.3cm. Flow rate 0.6 ml/min, stoptime 15 min, posttime 5 min.

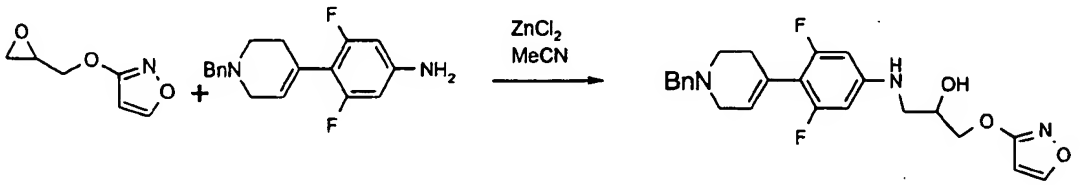
Isocratic: 40 % B. Wavelengh: 225 nm. Injection 2.5 ml. Sample solvent 50:50 MeCN:water.

Concentration up to 1mg/ml. Oven at 45°C.

The following solvents have also been used in the coupling reaction in place of Toluene :- MIBK, THF, Toluene, TBME.

Example 3 : Preparation of intermediates - Scheme 1C

Preparation of 1-[4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenylamino]-3-(isoxazol-3-yloxy)-propan-2-ol (Compound (IN))



To 3-(2,3-oxiranepropyloxy)isoxazole (2.5g, 17.7 mmol, 1.0 equiv) and zinc chloride (2.4g, 17.7 mmol) in acetonitrile (3.5 mL) was added 3,5-difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline (5.3 g, 17.7 mmol). The reaction mixture was stirred at ambient temperature for 4 hr. After this time HPLC showed 56% conversion to 1-[4-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenylamino]-3-(isoxazol-3-yloxy)-propan-2-ol (with reference to an external standard isolated in another reaction, which may be prepared by hydrolysis of Compound (IJ)).

HPLC : retention time (see below) 2.1 min.

Mobile phase A: 0.1% TFA in water. Mobile phase B: 0.1% TFA in 90 % MeCN.

Column: Genesis C18 10x0.3cm. Flow rate 0.6 ml/min, stoptime 15 min, posttime 5 min. Isocratic: 40 % B. Wavelengh: 225 nm. Injection 2.5 ml. Sample solvent 50:50 MeCN:water. Conc up to 1mg/ml. Oven 45°C.

Example 4 : Diol Chemistry - Scheme 2B

Intermediate Example 1: 3,5-Difluoro-4-(1-benzyl-4-hydroxyhexahydropyrid-4-yl)aniline

nBuLi (1.32M in hexanes, 350ml, 0.462 mol) was added dropwise over 20 minutes to a solution of N,N-(1,2-bis(dimethylsilyl)ethane)-3,5-difluoroaniline (108.4g, 0.40mol, J. Org. Chem., 60, 5255-5261 (1995)) in 800ml dry THF at -70°C under argon. After stirring for a further 4 hours at -70°C, N-benzyl-4-piperidone (87.8g, 0.46mol) in 270ml dry THF was added dropwise over 40 minutes at the same temperature and the reaction allowed to stir to ambient temperature overnight. Solvent was removed in vacuo and the resultant product treated with ice and conc.HCl and extracted with ether. The aqueous acidic phase was then treated with 40% NaOH with cooling, extracted with ether (and worked up by washing with water, with brine and drying with an anhydrous drying agent such as magnesium sulfate or sodium sulfate before evaporation - this work up procedure is referred to as work up in the usual manner hereinafter) to give 144.7g of a sludge. Analysis by TLC using 10% MeOH/dichloromethane on silica indicated that the desired alcohol was present as approximately 90% of the product, and the crude product was used without further purification. MS: ESP+ (M+H) = 319.

Intermediate Example 2: 3,5-Difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline

The crude product from Intermediate Example 1 (144.7g) was suspended in 400ml conc.HCl and heated at reflux with stirring for 18 hours. TLC showed all starting material had reacted, and after cooling in ice the reaction mixture was taken to pH 11 with conc. NH_3 (aq) and extracted three times with dichloromethane. Usual work-up gave 119.5g of a viscous oil. TLC indicated a purity of ca. 80% and the crude product was used without further purification. MS: ESP+ (M+H) = 301.

Intermediate Example 3: N-Benzyloxycarbonyl-3,5-difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline

The crude aniline from Intermediate Example 2 (3.2g, 10.7mmol) in 10ml of acetone was added in one portion to a stirred solution of sodium dihydrogen phosphate (3.0g) in 30ml water. The resulting mixture was cooled to 5-10°C and a solution of benzylchloroformate (2.18g, 1.8ml, 12.8mmol) in 10ml of acetone was added dropwise. The mixture was stirred for a further hour at ice-bath temperature and then at ambient temperature for 2 hours. The mixture was diluted with 80ml water, basified with conc.NH_3(aq) and extracted with EtOAc. Usual work-up gave a viscous oil which was purified by flash chromatography (Merck 9385 silica, EtOAc/isohexane (3:7 eluant) and triturated with isohexane to give a solid (1.53g 33%).
MS: ESP+ (M+H) = 434.

Intermediate Example 4: 5(R)-Hydroxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

The benzylurethane from Intermediate Example 3 (5.54g, 12.76mmol) in 50ml dry THF was cooled to -70°C under nitrogen and 8.80ml of 1.6M nBuLi in hexanes (14.08mmol) added dropwise at the same temperature. After 20 minutes at the same temperature a solution of (R)-glycidyl butyrate (2.00g, 13.88mmol in 5ml THF) was added dropwise and the mixture stirred for 30 minutes at -70°C, and then stirred to ambient temperature overnight. After quenching with 100ml 10% ammonium chloride, the mixture was extracted with EtOAc and usual work-up to give an oily solid, which was purified by flash chromatography (Merck C60 silica, 5% MeOH/dichloromethane eluant) to give a crystalline solid (4.40g, 86%).
MS: ESP+ (M+H) = 401.
^{1}H-NMR (250MHz, DMSO-d6): d = 2.32 (m, 2H), 2.63 (t, 2H), 3.05 (m, 2H), 3.50-3.72 (m,4H), 3.82 (dd,1H), 4.06 (t,1H), 4.73 (m,1H), 5.18 (t,1H), 5.78 (m,1H).

Intermediate Example 5: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Intermediate Example 4 (2.6g, 6.5mmol), 3-hydroxyisoxazole (see Example 1; 0.60g, 7.06mmol), triphenylphosphine (1.96g, 7.48mmol) and diisopropylazodicarboxylate (1.44g, 7.13mmol) in THF (40ml) were reacted using the general method of Example 1. The resultant

product was purified by flash chromatograpy (Merck 9385 silica, EtOAc / isohexane (3:2) eluant initially, then repeated using methyl tert-butylether eluant) to give the title product (2.6g, 86%) as a gum. MS: ESP$^+$ $(M+H)^+$= 468.

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (Compound (IK))

Intermediate Example 5 (2.6g, 5.57mmol) in dichloromethane (40ml) was cooled, under an atmosphere of nitrogen, in an ice-water bath then 1-chloroethyl chloroformate (0.80g, 5.59mmol) added dropwise via syringe. The resulting solution was stirred at ice temperature for 1 hour before isolating the intermediate product (carbamate) by flash chromatography (Merck 9385 silica, EtOAc / isohexane (1:1) eluant). The resulting gum was taken up in MeOH (40ml) and refluxed for 1 hour. Evaporation of the solvent after this time gave the title product (1.46g, 64%) as a crystalline solid.

^{1}H-NMR (300MHz, DMSO-d6): d = 2.54 (m, 2H), 3.27 (m, 2H), 3.72 (m, 2H), 3.92 (dd, 1H), 4.20 (t, 1H), 4.38-4.52 (m, 2H), 5.10 (m, 1H), 5.88 (m, 1H), 6.38 (d, 1H), 7.37 (m, 2H), 8.68 (d, 1H), 9.39 (s(broad), 2H). MS: ESP$^+$ $(M+H)^+$=378.

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-hydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (Compound (2I))

To a stirred solution of Compound (IK) (6.2g, 15mM), N-methyl morpholine (2.27g, 22.5mM), hydroxybenztriazole (2.63g, 19.5mM) and 3-t-butoxy-2(S)-hydroxypropionic acid (Compound (2H); WO Patent 92/00276; 3.16g, 19.5mM) in DMF (60ml) at ambient temperature, was added in portions, dimethylaminopropyl-ethylcarbodiimide (3.73g, 19.5mM). The reaction mixture was stirred for 3hrs.

The solvent was evaporated and the residue was taken into ethyl acetate. It was washed with 2N HCl, water, sat.$NaHCO_3$ and brine, dried over anh.Na_2SO_4 and evaporated to a gum. The title compound was isolated by MPLC (Merck 9385 silica, 60-75% ethyl acetate / isohexane gradient) and crystallised on trituration with ether (6.4g, 82%).

NMR (300Mz, DMSO-d6): δ = 1.11(2s, 9H), 2.34(2s, 2H), 3.43(m, 2H), 3.70(m, 2H), 3.93(d of d, 1H), 4.10(s, 1H), 4.20(t, 1H), 4.28(s, 1H), 4.46(m, 3H), 5.07(m, 2H), 5.88(s, 1H), 6.40(s, 1H), 7.37(d, 2H), 8.70(s, 1H). Mass: ES+ $(M+H)^+$ = 522.

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-(di-t-butoxyphosphoryl)-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (Compound (2J))

To a stirred solution of Compound (2I) (3.65g, 7.0mM) and tetrazole (2.21g, 31.5mM) in THF (50ml) at ambient temperature under nitrogen, was added $(t\text{-BuO})_2PNEt_2$ (2.61g, 10.5mM) over ~2mins. After stirring for 2hrs., more tetrazole (735mg, 10.5mM) and $(BuO)_2PNEt_2$ (872mg, 3.5mM) were added and stirring was continued for a further 1hr.

The solution was cooled to -40°C and m-chloroperbenzoic acid (14mM, 2.68g of 90% strength) was added in portions. The reaction mixture was allowed to warm to 0°C and ethyl acetate was added. The solution was washed with aq. sodium metabisulphite, sat. sodium bicarbonate and brine. The organic phase was dried over anh. Na_2SO_4 and evaporated under reduced pressure. The title compound was isolated by MPLC (Merck 9385 silica, 70-90% ethyl acetate / isohexane gradient) as a crisp foam (3.63g, 73%).

NMR (300Mz, DMS0-d6): δ = 1.10(2s, 9H), 1.40(2s, 18H), 2.35(m, 2H), 3.45 - 4.5(complex, 10H), 4.93(q, 1H), 5.10(m, 1H), 5.88(s, 1H), 6.40(s, 1H), 7.35(d, 2H), 8.70(s, 1H).

Mass: ES+ (M+H) = 714.

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (Compound (2F))

Compound (2J) (4.93g, 6.9mM) was dissolved in 4N HCl / dioxan (50ml) and the solution was stirred at ambient temperature for 21hrs. It was evaporated to a mobile oil and triturated well with ether to give the title compound as a hygroscopic, amorphous solid which was filtered off under nitrogen and dried under high vacuum (3.75g, 98%; HPLC purity=88%).

NMR (300Mz, DMS0-d6): 2.43 (m, partially obscured), 3.6 - 4.35 (m, 8H), 4.35 - 4.60 (m, 3H), 5.09 (m, 1H), 5.85 (s, 1H), 6.30 (s, 1H), 7.31 (d, 2H), 8.60 (s, 1H).

Mass: ES+ (M+H)=546.

Example 5 ; Diol Chemistry - Scheme 2A

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-cyclophosphoryl-propan yl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (Compound (2E))

To a stirred partial solution of the starting material, 5(R)-isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (38.13g, 82mM) and tetrazole (17.22g, 246mM) in THF (500ml) at ambient temperature under nitrogen, was added tert-butyl tetraethylphosphorodiimidite (30.5g, 123mM) over ~10mins. The reaction mixture was stirred for 30 min. at ambient temperature.

The solution was cooled to -40°C and m-chloroperbenzoic acid (134mM, 25.9g of 90% (t-strength) was added in portions. The reaction mixture was allowed to warm to 0°C and ethyl acetate was added. The solution was washed with aq. sodium metabisulphite, sat. sodium bicarbonate and brine. The organic phase was dried over anh. $MgSO_4$ and evaporated under reduced pressure. The title compound was isolated by MPLC (Merck 9385 silica, 90-100% ethyl acetate / isohexane gradient) as a gum. The product was used for the next step without further characterisation or delay (22.5g, 47%).

5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one (Compound (2F))

Compound (2E) (22.4g, 38.4mM) was dissolved in 4N HCl / dioxan (200ml) and water (0.69ml, 38.4ml) was added. The solution was stirred at ambient temperature for 18hrs. It was evaporated to a mobile oil and triturated well with ether to give the title compound as hygroscopic, amorphous solid which was filtered off under nitrogen and dried under high vacuum (18.7g, 89%; HPLC purity=87%).

NMR (300Mz, DMSO-d6): 2.43 (m, partially obscured), 3.6 - 4.35 (m, 8H), 4.35 - 4.60 (m, 3H), 5.09 (m, 1H), 5.85 (s, 1H), 6.30 (s, 1H), 7.31 (d, 2H), 8.60 (s, 1H).

Mass: ES+ (M+H)=546.

The starting material (Compound (2D)), 5(R)-isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one is obtained as follows :-

Intermediate Example 6 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2,2-dimethyl-1,3-dioxolan-4(S)-ylcarbonyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Compound (IK) (5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one; 660mg, 1.45mmol), (S)-2,3-O-isopropylidineglyceric acid (240mg, 1.64mmol) and pyridine (115mg, 1.45mmol) in dichloromethane (15ml) are stirred and 1,3-dicyclohexylcarbodiimide (315mg, 1.53mmol) is added in one go at ambient temperature. The resulting mixture is stirred at ambient temperature for 18 hr then purified by flash chromatography (Merck 9385 silica; EtOAc / isohexane (3:1) eluant) to give the product (282mg, 38%) as a colourless crystalline solid. MS: ESP^+ $(M+H)^+ = 506$.

^{1}H-NMR (300MHz, DMSO-d6): d = 1.32 (s, 3H), 1.34 (s, 3H), 2.25-2.50 (m, 2H), 3.63-3.87 (m, 2H), 3.95 (dd, 1H), 4.02-4.32 (m, 4H), 4.43-4.55 (m, 2H), 4.92 (m, 1H), 5.12 (m, 1H), 5.89 (m, 1H), 6.37 (d, 1H), 7.35 (d, 2H), 8.68 (d, 1H).

Compound (2D) : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-dihydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Intermediate Example 6 (282mg, 0.56mmol) in a mixture of THF (6ml) and 1N hydrochloric acid (2ml) is left to stand at ambient temperature for 4 days. The solvent is evaporated and the resulting product purified by flash chromatography (Merck 9385 silica; 10% MeOH in dichloromethane eluant) to give the product (183mg, 70%) as a colourless crystalline solid: mp 136-142 °C.

^{1}NMR (300MHz, DMSO-d_6): d = 2.20-2.46 (m, 2H), 3.40-3.63 (m, 2H), 3.63-3.85 (m, 2H), 3.92 (dd, 1H), 4.10 (m,1H), 4.18 (t,1H), 4.26-4.52 (m,1H), 4.68 (m,1H), 4.96 (m,1H), 5.10 (m,1H), (m,1H), 6.37 (d,1H), 7.34 (m,2H), 8.68 (d, 2H).

MS: ESP^+ $(M+H)^+ = 466$.

HPLC: Chiralpak AD (250mm x 4.6mm i.d.), 100% MeOH eluant, 1ml/min. flow rate: ret. time = 38.4 min.

CLAIMS

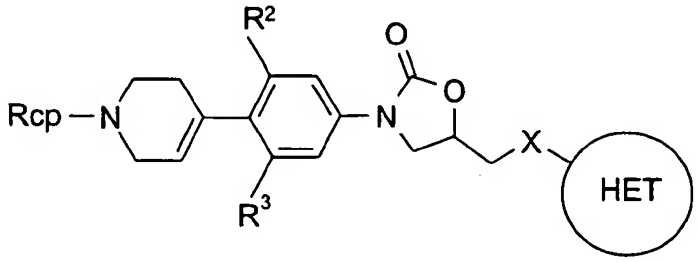
1. A process for the formation of a primary mono-phosphoryl (-$OPO(OH)_2$) group in a terminal 1,2-diol-propanoyl (HO-$CH_2CH(OH)$-CO-) functionality comprising the steps of

(i) formation of a protected primary 1,2-diol species (PgO-$CH_2CH(OH)$-CO-);

(ii) formation of a secondary phosphoryl group (optionally protected) and

(iii) treatment of this secondary phosphoryl group with acid to deprotect the protected primary alcohol function and rearrange the secondary phosphoryl group to a primary phosphoryl group (to give a $(HO)_2OPO$-$CH_2CH(OH)$-CO- functionality); wherein Pg is a protecting group.

2. A process as claimed in claim 1 wherein the terminal 1,2-diol-propanoyl functionality is present in a compound of the formula (I-2)



(I-2)

wherein

X is O or S;

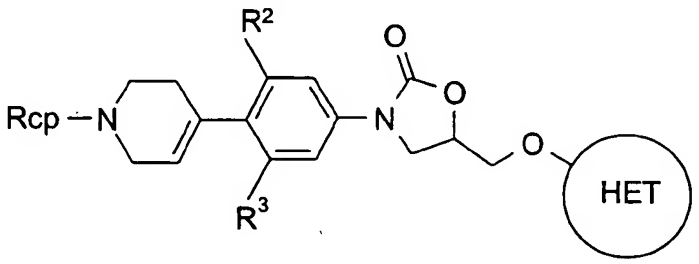
HET is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

HET is a C-linked 6-membered heteroaryl ring containing 1 or 2 N, which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

R^2 and R^3 are independently hydrogen or fluoro;

Rcp is of the formula $R^{13p}CO$- (wherein R^{13p} is (1-10C)alkyl substituted by two or more hydroxy groups; 2 of which are in a 1,2-diol orientation, ie. there is a terminal primary alcohol with an adjacent secondary alcohol), or pharmaceutically-acceptable salts, or in-vivo-hydrolysable esters thereof.

3. A process as claimed in claim 1 or 2 wherein the terminal 1,2-diol-propanoyl functionality is present in a compound of the formula (I)



(I)

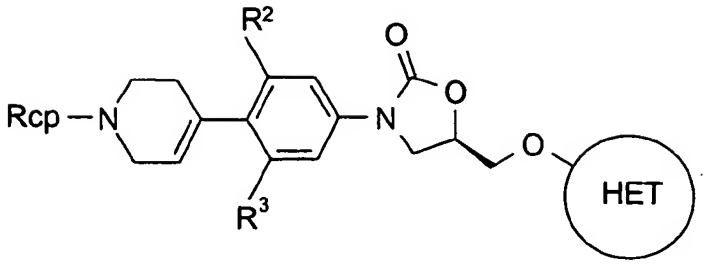
wherein

HET is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

R^2 and R^3 are independently hydrogen or fluoro;

Rcp is of the formula $R^{13p}CO$- (wherein R^{13p} is (1-10C)alkyl substituted by two or more hydroxy groups; 2 of which are in a 1,2-diol orientation, ie. there is a terminal primary alcohol with an adjacent secondary alcohol), or pharmaceutically-acceptable salts, or in-vivo-hydrolysable esters thereof.

4. A process as claimed in any one of claims 1 to 3 wherein the terminal-1,2-diol-propanoyl functionality is present in a compound of the formula (I-1)



(I-1)

5. A process as claimed in any one of claims 1 to 4, comprising

(i) the reaction of 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one with 3-t-butoxy-2(S)-hydroxypropionic acid to form 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-hydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one;

(ii) phosphorylation of this compound to give 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-(di-t-butoxyphosphoryl)-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one and

(iii) treatment of this compound with acid to give 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one.

6. A process as claimed in any one of claims 1 to 4 wherein in step (i) the protecting group is t-butyl.

7. A process as claimed in any one of claims 1 to 6 wherein step (ii) is carried out using tert-butyl tetraethylphosphorodiimidite.

8. A process as claimed in any one of claims 1 to 7 wherein step (iii) is carried out using hydrochloric acid.

9. A process for the preparation of 5-(HET-X-methyl)-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one comprising the reaction of (3-(2,3-

oxiranepropyl-X-HET with N-benzyloxycarbonyl-3,5-difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline; wherein X and HET are as defined in claim 2.

10. A process as claimed in claim 9 for the preparation of 5-Isoxazol-3-yloxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one comprising the reaction of (3-(2,3-oxiranepropyloxy)isoxazole with N-benzyloxycarbonyl-3,5-difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline.

11. A chemical intermediate compound selected from
5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-hydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one and
5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-(di-t-butoxyphosphoryl)-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one.

12. A chemical intermediate compound selected from
3-(2,3-oxiranepropyloxy)isoxazole and
5-Isoxazol-3-yloxymethyl-3-(3,5-difluorophenyl)oxazolidin-2-one.

13. A chemical intermediate compound selected from
5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-cyclophosphoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one and
1-[4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenylamino]-3-(isoxazol-3-yloxy)-propan-2-ol.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2001 (07.06.2001)

PCT

(10) International Publication Number
WO 01/40236 A3

(51) International Patent Classification[7]: C07F 9/09, 9/6558, C07D 413/14, 413/12, C07F 9/6574

(21) International Application Number: PCT/GB00/04527

(22) International Filing Date:
28 November 2000 (28.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9928499.4 3 December 1999 (03.12.1999) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/40236 A3

(54) Title: PHOSPHORYLATION OF TERMINAL PRIMARY ALCOHOL GROUPS

(57) Abstract: The invention relates to chemical processes and chemical intermediates which are useful in the selective formation of a primary mono-phosphoryl group (-OPO(OH_2)) in a terminal 1,2-diol-propanoyl (HO-CH_2CH(OH)-CO-) containing system, and to chemical processes and chemical intermediates (and processes for their manufacture) particularly useful for the manufacture of anti-Gram positive oxazolidinone bacterial agents containing such functionality, in particular for the preparation of 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S) -hychoxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-il)3,5-difluorophenyl)oxazolidin-2-one.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/04527

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/09 C07F9/6558 C07D413/14 C07D413/12 C07F9/6574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BUCHWALD S.L.: "Stereochemical evidence for pseudorotation in the reaction of a phosphoric monoester" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 106, no. 17, 1984, XP002162618 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 abstract and scheme 1 ---	1
A	MEYERHOF O.: "Über die Isolierung der isomeren Phosphoglycerinsäuren." BIOCHEMISCHE ZEITSCHRIFT., vol. 276, 1936, pages 239-253, XP000989557 SPRINGER, BERLIN., DE ISSN: 0366-0753 page 244 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2001	11 07 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/04527

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIS K.: "Biosynthesis of riboflavin." BIOCHEMISTRY., vol. 34, no. 9, 1995, pages 2883-2892, XP002162619 AMERICAN CHEMICAL SOCIETY. EASTON, PA., US ISSN: 0006-2960 figure 3 ---	1
P,A	WO 99 64417 A (ZENECA LTD.) 16 December 1999 (1999-12-16) page 65, line 25 -page 70, line 8	1-8,11
P,X	example 154; page 185, step (i) and compound IV; page 36, lines 5-6 -----	9,10,12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/04527

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8,11

A process for preparing primary monophosphoryl derivatives of a terminal 1,2-diol compound. Intermediates therefor when the process is used for preparing particular derivatives as described in WO 99 64417.

2. Claims: 9,10,12(in part)

A process for preparing certain heterocyclic compounds described in WO 99 64417, by using as starting material an oxirane derivative. The starting material named 3-(2,3-oxiranepropyloxy)isoxazole.

3. Claim : 12(in part)

The intermediate compound named 5-Isoxazol-3-yloxymethyl-3-(3,5-difluorophenyl)oxazolidin-2-one

4. Claim : 13(in part)

The intermediate compound named 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S),3-cyclophosphoryl-propanoyl)-1,2,5,6-tetrahydropyridyl-4-yl)-3,5-difluorophenyl) oxazolidin-2-one

5. Claim : 13(in part)

The intermediate compound named 1-(4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenylamino)-3-(isoxazol-3-yloxy)-propan-2-ol

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/04527

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9964417 A	16-12-1999	AU 4157199 A	30-12-1999
		BR 9910971 A	13-02-2001
		EP 1082323 A	14-03-2001
		NO 20006152 A	02-02-2001